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Prenatal exposure to PCBs and neurological and sexual/ pubertal development from birth to adolescence

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Several chemical compounds are resistant to degradation and end up in the food chain. One group of these chemicals is polychlorinated biphenyls (PCBs) which are used as flame retardants and plasticizers. Although PCBs were banned several decades ago, PCBs are still found in environmental media, including in the body of humans. PCBs are transferred from mother to fetus via the placenta during pregnancy. Considering that the prenatal period is a sensitive period during which essential developmental processes take place, exposure to environmental chemicals might have considerable and permanent consequences for outcomes in later life.

The aim of this review is to provide an update on the latest insights on the effects of prenatal exposure to PCBs on neurological, sexual and pubertal development in children. We give an overview of recent literature, and discuss it in the light of the findings in a unique Dutch birth cohort, with data on both neurological and pubertal development into adolescence.

The findings in the studies included in this review, together with the findings in the Dutch cohort, demonstrate that prenatal exposure to PCBs can interfere with normal child development, not only during the perinatal period, but up to and including adolescence. Higher prenatal exposure to PCBs was found to be both negatively and positively associated with neurodevelopmental outcomes. Regarding pubertal development, higher prenatal PCB exposure was found to be associated with more advanced pubertal development, also in the Dutch cohort, whereas other studies also found delayed pubertal development. These findings raise concern regarding the effects of man-made chemical compounds on child development. They further contribute to the awareness of how environmental chemical compounds can interfere with child development and negatively influence healthy ageing.

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Introduction

Environmental chemicals

In the past decades, various classes of chemicals were produced that were used in a wide variety of consumer products, such as coolants in electrical appliances and flame retardants in a range of household items. Two examples of such chemicals are polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs). These organohalogens have proved useful as flame retardants on account of their resistance to high temperatures. After two incidents with PCB-contaminated rice oil, awareness of the potential toxic effect of exposure to PCBs increased.[1,2] Chemicals like PCBs are known as persistent organic pollutants (POPs) because they continue to exist in the environment for long periods because of their resistance to chemical and biological degradation.[3] On account of the growing concern about their toxicity and persistence, the production and use of several POPs have been reduced or banned altogether.

Polychlorinated biphenyls

PCBs belong to a class of chemicals consisting of 209 different congeners with varying numbers of chlorine atoms attached to a biphenyl at varying positions.[4] (Fig. 1) PCBs can be metabolized in the human liver by microsomal oxidases to form hydroxylated metabolites (OH-PCBs). The OH-PCBs are present in concentrations in the human body similar in range to many PCB congeners.[5] PCBs were produced between 1929 and 1985 and were used in a variety of products including coolants in heat-transfer systems, lubricants in plastics and flame-retardants.[6] For examples of applications of PCBs see Fig. 2.[7,8]

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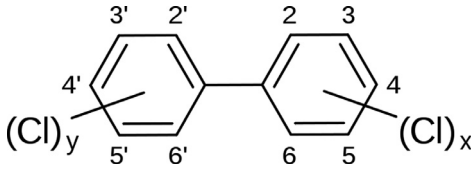

Fig. 1. Chemical structure of polychlorinated biphenyl congeners.

Legislation around the world

The commercial production of PCBs first began in 1920, and after 1945 production reached substantial volumes. It peaked in the 1960s and 1970s.[9] In the 1970s, owing to severe concerns pertaining to their human toxicity, suspected carcinogenicity, and environmental persistence, several countries limited the use of PCBs. Finally in 1985, the use of PCBs was heavily restricted in the European Community. However, it appeared that due to the persistence of PCBs, humans continued to be exposed to the contaminating effects of these compounds and restrictions in use did not imply decreases in exposure.

Internationally, there came a call for action to reduce and eliminate the use and release of PCBs in the environment. In Europe, two international legally binding instruments have been negotiated. These were the 1998 Aarhus Protocol on Persistent Organic Pollutants (POPs) from the regional United Nations Economic Commission for Europe Convention (entered into force on 23rd of October 2003), and the Global Stockholm Convention on POPs (entered into force on 17 May 2004).[10] The protocols aimed at disposing completely of PCBs and equipment of PCBs as soon as possible. They included provisions for dealing with the wastes of products that were banned. In addition, a council directive of the European Committee[11] that was incorporated into law in 1998, advised member states to make an inventory of big equipment containing PCBs, and to adopt a plan for disposal of this large equipment. It also provided outlines for collection and disposal of non-inventoried equipment (f.i. small electrical equipment very often present in household appliances manufactured before the ban on marketing of PCBs). For example, it was mandated that member states of the European Commission had to dispose of big equipment (equipment with PCB volumes of more than 5 liters) by the end of 2010 at the latest.

In the United States, the Environmental Protection Agency (EPA) was involved in the legislation on PCBs. From 1980 onwards, they issued interim guidance for the determination of penalties for violations of the polychlorinated biphenyl rules. In addition, the EPA provided PCB regulations on the cleanup and disposal options for PCB remediation waste in the US.

Research regarding levels of PCBs in different countries found that PCBs can be transported over long distances. Studies showed that PCBs could be detected in different areas all around the globe, including places far from where they were manufactured or used. PCBs are still found in measurable levels in all environmental media (soils and sediments, water, air, food), in wildlife, and also probably in the body of every human.

Exposure to PCBs in children

For humans the main routes of exposure to PCBs are through ingesting contaminated food, inhaling contaminated air and dermal absorption (Fig. 2).[4,12]

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PCBs accumulate in the food chain and are stored in fatty tissue. Therefore, the main source of dietary exposure to PCBs is through eating fish, meat and dairy products (Fig. 2).[7,8] Inside dwellings the concentration of PCBs can rise as a result of their leaking from household appliances, such as televisions and refrigerators, or on account of PCBs contained in construction materials, such as caulk and flame retardant coatings.[4,12]In addition

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PCBs have been detected in cord blood,[14] but breastmilk is an additional route of exposure to these organohalogens in the young infant.[15]

Chemical exposure levels differ around the world on account

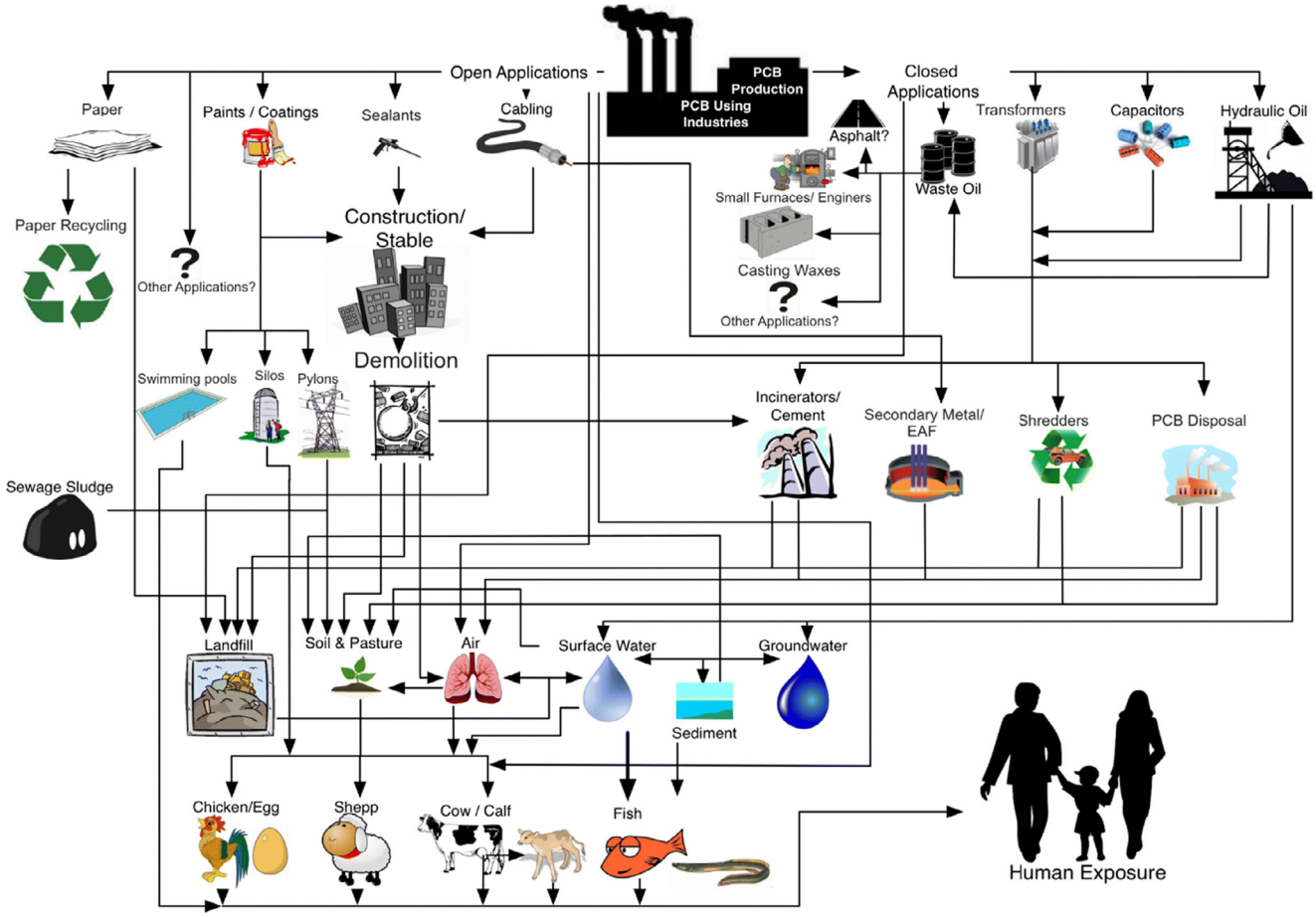

Fig. 2. Life cycle of PCBs showing environmental release sources and exposure pathways for food-producing animals. Figure adapted from Weber (2018)[8] https://doi.org/http://creativecommons.org/licenses/by/4.0/ which was adapted from Weber (2015).[7]

of, for example, accidental releases, eating habits and the time span between the production and banning of the chemicals. But it is also known that PCB congener patterns in the general population are different from the patterns found in commercial PCB products.[16] This may be explained by the fact that the general population is exposed to multiple sources of PCBs and not one single product. Exposure via inhalation leads to selective exposure to the more volatile, less chlorinated and less persistent congeners. Genetic differences in metabolic activity in humans also may play a role in these different levels.[9]

For this reason it is important to compare the different background levels (such as the Dutch levels) with levels measured in other countries. Because the quantification of exposure levels differs between studies, it is difficult to compare the PCB exposure levels. Longnecker and colleagues attempted to compare the exposure levels of ten studies after expressing PCB-153-levels in maternal pregnancy serum in a uniform manner.[17] They concluded that the exposure levels found in recent US studies were about one-third of those in recent studies in the Netherlands, Germany, and in northern Québec, Canada. Compared with most other studies, the exposure levels in the Faroe Islands study were about three-fold to four-fold higher on account of the traditional habit of eating pilot whale blubber that contains PCBs.

The World Health Organization (WHO) and United Nations Environmental Programme (UNEP) have performed surveys in breastmilk worldwide as part of a POPs monitoring plan under the Stockholm Convention. Fig. 3 shows the sum of detected indicator PCBs (PCBs 28, 52, 101, 138, 153 and 180) expressed as the sum of these PCBs in human milk samples from different countries.[18] It shows that particularly in the Czech Republic and Slovakia levels are far above the level that has been established

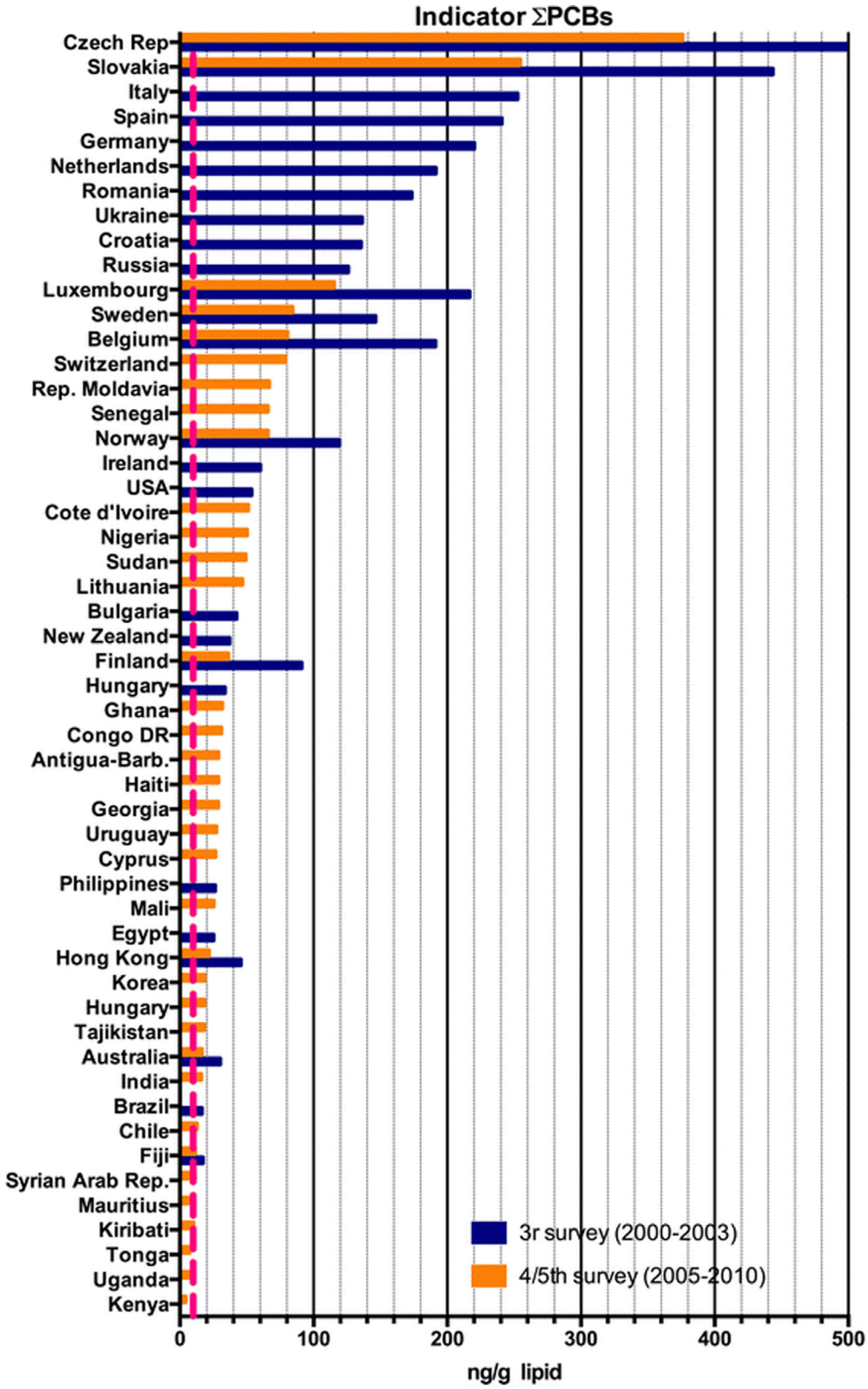

Fig. 3. The Sum of the indicator PCBs in ng/g lipid in pooled human milk samples from different countries (source WHO/UNEP surveys). The dotted line represents safe level of these compounds in breast milk. Figure adapted from van den Berg et al. 2017[18] https://doi.org/http://creativecommons.org/licenses/by/4.0/.

as safe. However, in basically all European countries and Russia, PCB levels in breastmilk are above the level considered as safe.

In basically all European countries and Russia, PCB levels in breastmilk are above the level considered as safe.

PCBs and brain development

PCBs are known to act as endocrine disrupters. Disruption of the thyroid hormone metabolism is one of the suggested mechanisms by which PCBs can affect neurodevelopment. Besides interference with endocrine mechanisms, there is growing evidence for interference of environmental chemicals with epigenetic mechanisms.

In the pre- and postnatal period, major processes of brain development and maturation take place. Neuronal formation and migration peak between the 12th and 20th week of gestation and are largely completed by 26 to 29 weeks of gestation.[19] Synaptogenesis starts as early as 5 weeks gestation, and continues throughout gestation. It gives rise to the subplate between 18 and 22 weeks gestation, and leads to the formation of early neuronal circuits.[20] Myelination starts prenatally by the formation of myelin by oligodendrocytes. It begins in the subcortical regions and later the cortical regions become myelinated. Between gestational age weeks 36 and 40, the proportion of total brain volume that contains myelinated white matter increases from 1 to 5%.[21] Myelination and formation of neuronal circuits continue into infancy and childhood, until early adolescence. These key processes in brain development form the basis of later neurodevelopmental outcome.

PCBs are found to interfere with functioning of several systems, including the developing central nervous system, reproductive system and immunological system. Their interference with normal central nervous system development occurs mainly through thyroid and neurotransmitter disruption.[22–24] Disruptions of these systems have been linked to neurodevelopmental impairments in children exposed to high levels of organohalogens.

Thyroid hormones play a central role in brain development and function. For example, thyroid hormones increase the rate of stem cell proliferation and stimulate neuronal differentiation. [25] Once new neurons begin differentiating, the cells follow an orderly pattern of migration to the appropriate areas in the brain. Deficiency in thyroid hormones has been shown to cause disorganization of brain structure.[26] Thyroid hormones also stimulate formation and development of neurons, including axons and dendrites.[27] PCBs, amongst other environmental pollutants, have been shown to alter thyroid function in wildlife species,[28] experimental animals, and in humans.[29]

PCBs may affect thyroid hormone homeostasis by interfering with thyroid hormone signaling in the developing brain, by changing intracellular thyroid hormone availability, and by interacting directly at the level of the thyroid hormone receptors.[30] Also, PCBs have a high affinity of binding to transthyretine, a protein that normally binds thyroid hormone.[31] This protein is essential for T4 transport to the brain.[32]

In addition to the effects on thyroid homeostasis, PCBs also have been shown to interfere with several neurotransmitters, such as dopamine, norepinephrine[33] and the serotonine system,[34] thereby altering brain functioning.

PCBs and neurodevelopmental outcome

Considering that the prenatal period is a sensitive period during which essential developmental processes take place, exposure to environmental chemicals might have considerable and permanent consequences for outcomes in later life. Evidence exists that fetuses and children are more susceptible to the harmful effects of PCBs than adults.

With regard to the neurological development of children, there is a growing body of evidence that even low-level environmental exposure to several POPs, including PCBs, might have neurotoxic effects. Associations have been found between exposure to PCBs and motor and cognitive function. For example OH-PCB-153 is related to lower scores on the mental scale of the Bayley Scales of Infant Development II in children at 18 months.[35] It has also been related to motor scores in children at 6 years of age.[36] Others reported effects of prenatal PCB exposure on neurologic performance and cognitive development at 6−11 years of age.[37–41] In addition, relations with behavioral disorders such as Autism Spectrum Disorder have been described.[42]

Pubertal development

Next to the endocrine disrupting effects on the central nervous system, PCBs have been related to pubertal

development, reproductive problems in males and females, obesity, diabetes, and endocrine related cancers.

During the last decades, a secular trend has been observed towards earlier pubertal timing, and endocrine disrupting chemicals might be a possible explanation.[43] Because puberty is the period during which major hormonal changes take place, endocrine disruptors might impair normal pubertal development in adolescents. Pubertal timing, both early and late maturation, has been linked to mental health problems.[44] Earlier timing of adrenarche, the earlier phase of pubertal development involving onset of development of pubic hair, was also found to be associated with a higher incidence of mental health problems, and brain development might possibly play a role in this relation.[45] Relations have not only been found between pubertal development and mental health problems at adolescence, but also with cancer risk in later life. For example, an earlier onset of pubertal development in girls was found to be related to breast cancer.[46,47] In boys, early onset of puberty was found to be related to testicular cancer.[48]

Aim of review

The aim of this review is to provide an update on the latest insights on the effects of prenatal exposure to PCBs on neurological, sexual and pubertal development in children. We provide an overview of recent studies. Because studies on the long-term effects of prenatal exposure to PCBs are scarce, we will discuss the recent literature in the light of the findings in our unique Dutch birth cohort, which has data on both neurological and pubertal development into adolescence. We hope that this overview will give a better understanding of this topic within the field of pediatric environmental health, and that it will bring awareness of the impact of environmental factors on child development.

Methods

Search strategy

We used PubMed for identifying studies that analyzed the association between prenatal exposure to PCBs and OH-PCBs and neurodevelopmental and sexual/pubertal outcomes in children. Our search strategy included a combination of four general search terms: chemical terms (PCB, PCBs, polychlorinated biphenyl, OH-PCB, OH-PCBs, hydroxylated polychlorinated biphenyl, hydroxy polychlorinated biphenyls), a search term for timeframe of chemical exposure (prenatal, maternal, serum pregnancy, cord, placenta or placental combined with one of the following terms: serum, blood, plasma, exposure or level), a search term for the study population (child, children, infant, infants, toddler, toddlers, neonate, school age, adolescent, 11-year-old, 12-year-old, 13-year-old, 14-year-old, 15-year-old), and a search term for neurodevelopmental outcome (neuro, neurotoxic, neurodevelopment, neurologic, neurobehavioural, motor development, motor repertoire, cognitive development, cognition, IQ, intelligence quotient, intelligence, neuropsychological, behavior, ADHD, attention deficit hyperactivity disorder, ASD, autism spectrum disorder, autism, attention, inattention, hyperactivity), or on sexual/pubertal outcome (sexual development, reproductive health, reproductive hormone, reproductive hormones, pubertal development, testes, testes volume, Tanner stage, pubertal stage, breast development, pubic hair, menarche, pubertal characteristics, sex hormones, testosterone, estradiol, LH, luteinizing hormone, FSH, follicle stimulating hormone, Inhibin B, AMH, anti-müllerian hormone). This review is restricted to human studies of which a full text was available on PubMed on the 1st of October 2018. Regarding studies on neurodevelopmental outcome, this review was restricted to studies published after the 1st of October 2014. Findings on studies before the 1st of October 2014 were described in our previous review.[49]

Description of longitudinal Dutch cohort study

In this review we describe in more detail the findings regarding the effects of prenatal exposure to both PCBs and OH-PCBs on child development in the prospective longitudinal observational studies in two Dutch birth cohorts. The first cohort consisted of 104 mother-infant pairs included between 1998 and 2000 in the RENCO study (Risk of Endocrine Contaminants on Human Health study).[13] The second cohort consisted of 90 mother-infant pairs included between 2001 and 2002 in the GIC study (Groningen Infant COMPARE study, which stands for Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens).[50] Pregnant women in the northern part of the Netherlands were invited to participate by their midwife or obstetrician. The

mothers were of western European origin and had no serious illnesses or complications during pregnancy or delivery. All children were singletons, and born full term at 37−42 weeks' gestation without congenital anomalies or diseases. Maternal serum samples were collected during the second and/or third trimester of pregnancy in both cohorts. In all these samples the levels of PCB-153, 4-OH-PCB-107, 4-OH-PCB-146, and 4-OH-PCB-187 were determined. In the RENCO study, nine other PCBs (105, 118, 138, 146, 156, 170, 180, 183 and 187) and three other OH-PCBs (3-OH-PCB-153, 3'-OH-PCB-138 and 4'-OH-PCB-172) also were measured.

Results and discussion

Neurotoxic effects of prenatal exposure to (OH-) PCBs during childhood

Previously, we presented an overview of literature, published and available online on the 1st of October in 2014, on the relationship between various POPs and childhood neurodevelopmental outcomes.[49] The findings demonstrated that exposure to environmental chemicals can affect neurological development and behavioral outcomes in children in several domains, including attention, motor development and mental development. Regarding the exposure to PCBs and OH-PCBs, most studies reported inverse associations with neurodevelopmental outcomes. A suggested potential mechanism through which POPs may have an adverse effect on neurological development is through interference with thyroid hormone signaling in the developing brain as is outlined in the introduction. The previous overview also showed that several studies found that boys were more vulnerable to the harmful effects of exposure to environmental chemicals than girls. A possible explanation for this sex-related difference could be that these chemical compounds act as androgen or estrogen receptor antagonists or agonists and thereby affect the development of boys differently.

In Table 1 we provide an overview of literature which has been published during the last 4 years on the effects of prenatal exposure to PCBs and neurodevelopmental outcomes in children (Table 1). Similar to findings in studies published between 2004 and 2014, recent published studies also show significant associations between prenatal exposure to PCBs and neurological outcomes, predominantly suggesting negative effects on child development. Out of the 18 studies published since October 2014, 12 studies reported one or more negative effects of prenatal exposure to PCBs on outcome measures in children (Table 1). Five studies reported besides negative associations also positive associations, suggesting a more optimal development after higher exposure.[35,51−54] Six out of the 18 studies did not find any significant association between prenatal exposure to PCBs and the outcome measures (Table 1).

With regard to outcomes in children at preschool age, predominantly negative effects were found of prenatal exposure to PCBs. In Japanese boys, maternal pregnancy serum levels of 5 individual and the sum of 8 mono-ortho PCBs and the sum of the measured co-planar PCBs were negatively associated with psychomotor development at 6 months of age.[51] In girls from the same study, one mono-ortho PCB was negatively associated with psychomotor development at 6 months of age, whereas one non-ortho PCB and 4 mono-ortho PCBs were positively associated with psychomotor development at 18 months.[51] In Korean toddlers, associations were found between higher maternal serum levels of PCBs, including PCB-153, and more behavioral problems, including in externalizing behavior.[55] In a large cohort in Norway, including 44,092 mother-child pairs, the estimated maternal dietary exposure to PCBs during pregnancy was found to be associated with parent-reported language delay in the children at three years of age.[56] The study reported more associations between estimated prenatal PCB exposure and language development in girls, compared with boys. In girls, higher estimated dietary exposure to dl-PCBs and/or PCB-153 was found to be associated with less optimal performances on grammar, communication skills and with language delay, whereas in boys an association was found with less optimal performance on grammar, as reported by the parents. The link between higher estimated maternal dietary exposure to PCBs and poorer language skills in girls was also suggested by findings in another study, including part of the mentioned Norwegian cohort (n=1,024). [57] Girls born to mothers with higher estimated dietary exposure to dl-PCBs and PCB-153 had lower scores on expressive language, as reported by pre-school teachers.[57] In Japanese children at the age of 42 months, higher maternal serum levels of PCBs were found to be positively associated with cognitive development.[52] Sex-specific effects have been

TABLE 1. Overview of recent studies on the effects of prenatal PCB- and OH-PCB exposure on neurodevelopment in children.

Reference	Location	Sample age at evaluation	n with prenatal PCB data	Prenatal sample	PCB levels	Outcome measures	Results	No 'X', negative '↓' or positive '↑' effects on child outcome[a]
Nakajima et al. [51]	Japan	6 and 18 months	190 (6 months) 121 (18 months)	- Maternal serum during pregnancy - 4 non-ortho PCBs; 8 mono-ortho PCBs	Median Σ non-ortho PCBs: 83.9 pg/g lipid (IQR: 61.3, 110.3) Median Σ mono-ortho PCBs: 12,115.8 pg/g lipid (IQR: 7775.9, 15,677.0) Median Σ co-planar PCBs: 12,203.5 pg/g lipid (IQR: 7851.5, 15,790.0)	Bayley Scales of Infant Development-2nd Edition (BSID-II)	♂: 5 individual and Σ mono-ortho PCBs, and Σ co-planar PCBs were negatively associated with PDI at 6 months ♀: 1 mono-ortho PCB negatively associated with PDI at 6 months ♀: 1 non-ortho PCB and 4 mono-ortho PCBs positively associated with PDI at 18 months	♂: ↓ ♀: ↑ & ↓
Kim et al. [55]	Korea	13−24 months	59	- maternal serum during pregnancy - 19 PCBs	Median ΣPCBs: 27.3 ng/g lw (IQR: 15.7, 34.5)	- BSID-II - Social Maturity Scale (SMS) - Child Behavior Checklist (CBCL)	Higher maternal PCB-153 and ΣPCBs associated with more externalizing and total problems on CBCL	↓
Ruel et al. [35]	The Netherlands	18 and 30 months	181 (18 months) 63 (30 months)	- maternal serum during pregnancy - PCB-153 and 3 OH-PCBs in all samples - 9 other PCBs and 3 other OH-PCBs in part of samples	Median Σ10PCBs: 296.8 ng/g lw (IQR: 217.5, 391.1) Median PCB-153: 88.0 ng/g lw (IQR: 68.8-144.0) Median Σ6OH-PCBs: 388.5 pg/g fresh weight (IQR: 275.8, 546.3)	- BSID-II	Higher exposure to PCB-153 was marginally significant associated with delayed MDI scores at 18 months in one cohort (not in combined cohort) At 18 months higher exposure to 4-OH-PCB-187 in one cohort correlated with a lower MDI score At 30 months higher exposure to four individual OH-PCBs and the ΣOH-PCBs correlated with a higher MDI and a trend was seen for one OH-PCB	↓ & ↑
Caspersen et al. [56]	Norway	3 years	44.092	- Estimation of exposure to 12 dl-PCBs and 6 non-dioxin-like PCBs by combining information about food consumption from the food frequency questionnaire with a database of levels of dl-PCBs in Norwegian food	Estimated median dl-PCBs (total TEQ): 0.6 pg/kg bw/day (range: 0.06-16) Estimated median PCB-153: 0.7 ng/kg bw/day (range: 0.05-28)	- Dale and Bishopgrammar rating - Ages and Stages communication scale (ASQ)	♂+♀: High maternal exposure to dl-compounds (>14pg TEQ/kg bw/week) and to PCB-153 (>P97.5) was associated with higher odds of incomplete grammar ♀: dl-compounds associated with severe language delay ♀: high exposure to dl-compounds and PCB-153 was associated with moderate language delay ♀: high exposure to dl-compounds with low scores on ASQ	↓

(*continued on next page*)

TABLE 1. (*Continued*)

Reference	Location	Sample age at evaluation	n with prenatal PCB data	Prenatal sample	PCB levels	Outcome measures	Results	No 'X', negative '↓' or positive '↑' effects on child outcome[a]
Caspersen et al. [57]	Norway	3.5 years	1024	- Estimation of exposure to 12 dl-PCBs and 6 non-dioxin-like PCBs by combining information about food consumption from the food frequency questionnaire with a database of levels of dl-PCBs in Norwegian food	Estimated median exposure to dl-compounds: 0.56 pg TEQ/kg bw/day (IQR: 0.42−0.76) Estimated median exposure to PCB-153 was 0.81 ng/kg bw/day (IQR: 0.53−1.32)	- Preschool Age Psychiatric Assessment interview (PAPA) - Stanford-Binet 5th revision (SB-5) - Child Development Inventory (CDI); - Behavior Rating Inventory of Executive Function, Preschool version (BRIEF-P)	♀: higher exposure to dl-compounds and PCB-153 was associated with lower expressive language score	♀: ↓
Ikeno et al. [52]	Japan	42 months	141	- maternal serum during pregnancy - 4 non-ortho PCBs; 8 mono-ortho PCBs	Median Σ non-ortho PCBs: 84.6 pg/g lipid (IQR: 59.2, 113.2) Median Σ mono-ortho PCBs: 12,060.8 pg/g lipid (IQR: 8028.6, 17,656.4) Median Σ co-planar PCBs: 12,119.9 pg/g lipid (IQR: 8100.8, 17,762.6)	Kaufman Assessment of Battery for Children (K-ABC)	♂+♀: 1 non-ortho PCB and 4 mono-ortho PCBs were positively associated with achievement score (AS) ♀: 3 non-ortho PCBs, 7 mono-ortho PCBs, total non-ortho, total mono-ortho and total coplanar PCBs and all TEQ levels were positively associated with AS ♂: total non-ortho PCBs were negatively associated with the Mental Processing Composite Score	♂: ↓ ♀: ↑
Kyriklaki et al. [58]	Greece	4 years	689	-maternal serum during pregnancy - 6 PCBs (118, 153, 138, 156, 180, 170)	Median Σ6 PCBs: 320.8 pg/ml (IQR: 217.3, 484.8)	- McCarthy Scales of Children's Abilities. - Strengths and Difficulties Questionnaire - Attention Deficit Hyperactivity Disorder Test	High exposure to PCBs (≥P90) was associated with a reduction in working memory score	↓
Verner et al. [59]	Canada, Quebec	4-6 years	98	- cord plasma - PCB-153	Mean cord plasma PCB-153: 122 ng/g lipids (range 22−490)	- Inattention and activity were assessed by coding of video recordings of children undergoing fine motor testing	Cord plasma PCB-153 levels were not associated with inattention or activity	X
Hoyer et al. [60]	Ukraine, Poland and Greenland	5-9 years	1103	- maternal serum during pregnancy - PCB-153	Median PCB-153 Greenland: 107 ng/g lipid (P10-P90: 30−369) Ukraine: 27 ng/g lipid (P10-P90: 11−54) Poland: 11 ng/g lipid (P10-P90: 3−24)	- Developmental Coordination Disorder Questionnaire - retrospective parental reports of age at reaching developmental milestones in infancy	Medium tertile PCB-153 exposure was positively associated with age at standing and walking, corresponding to approximately two weeks delay, compared to children with lowest exposure tertile	↓

(*continued on next page*)

TABLE 1. (*Continued*)

Reference	Location	Sample age at evaluation	n with prenatal PCB data	Prenatal sample	PCB levels	Outcome measures	Results	No 'X', negative '↓' or positive '↑' effects on child outcome[a]
Rosenquist, et al. [61]	Greenland and Ukraine	5-9 years	1018	- maternal serum during pregnancy - PCB-153	Median PCB-153: 107 ng/g lipids (P10-P90: 30−369)	- Strengths and Difficulties Questionnaire	Prenatal PCB-153 exposures were non-significantly positively associated with abnormal conduct problem scores	X (↓)
Zhang et al. [62]	USA, Cincinnati	5 and 8 years	203 (5 years) 239 (8 years)	- maternal serum during pregnancy - 36 PCBs - Σ4 PCBs (118, 153, 138, 158)	Median Σ4 PCBs: 31.30 ng/g lipid	At 5 years: - Woodcock-Johnson Tests of Achievement III At 8 years: - Wide Range Achievement Test-4 - Wechsler Intelligence Scale for Children-IV - Behavioral Assessment System for Children-2	Prenatal Σ4 PCBs was not associated with a child's reading skills, FSIQ, and externalizing behavior problems	X
Orenstein et al. [63]	USA, New Bedford	7-11 years	393	- cord serum - 51 PCBs - Σ 4 PCBs: 153, 118, 138, 180 - TEQ of 5 dioxin-like PCBs: 105, 118, 156, 167, and 189	Mean Σ4 PCBs: 0.3 ng/g serum (range: 0.01-4.4) Mean dioxin-like PCBs: 1.5 pg TEQ/g lipid (range: 0-42.8)	- Wide Range Assessment of Memory and Learning	No associations between PCBs and WRAML indices	X
Verner et al. [64]	USA, New Bedford	7-11 years	441	- cord serum - 51 PCBs - PCB-153	Median PCB-153: 38 ng/g lipids	- Conners' Rating Scale for Teachers	Cord serum PCB-153 levels were associated with the DSM-IV Total and Hyperactive-Impulsive Index and Conners' ADHD index in quantile regression models at the 75th percentile	↓
Neugebauer et al. [53]	Germany, Duisburg	8-10 years	114	- maternal blood during pregnancy - 3 non-dioxin-like PCBs (138, 153, 180), 12 dioxin-like PCBs	Median $\Sigma PCB_{138,153,180}$: 0.16 μg/g lipid base (range: 0.03-1.81) Median WHO_{2005}-TEq ΣPCBs: 6.64 pg/g lipid base (range: 1.43-25.47)	- computer-based test battery of attention performance (KITAP) parent rating - questionnaire of behaviors related to ADHD (FBB-ADHS; a higher score indicate more ADHD-related behavior)	Increasing prenatal levels of WHO_{2005}-TEq ΣPCB were associated with a higher number of omission errors in the subtest Divided Attention $\Sigma PCB_{138,153,180}$ was positively associated ($P \leq 0.1$) with the number of false alarm responses in the Distractibility subtest WHO_{2005}-TEq ΣPCB was negatively associated with FBB-ADHS total and hyperactivity subscale $\Sigma PCB_{138,153,180}$ was negatively associated with FBB-ADHS hyperactivity subscale	↓ & ↑

(*continued on next page*)

TABLE 1. (*Continued*)

Reference	Location	Sample age at evaluation	n with prenatal PCB data	Prenatal sample	PCB levels	Outcome measures	Results	No 'X', negative '↓' or positive '↑' effects on child outcome[a]
Jacobson et al. [65]	Canada, Quebec, Nunavik	8-14 years	241	- cord plasma - PCB 153	Mean PCB-153: 120.3 ng/g lipid (range: 9.7−653.6)	- 7 subtests of the Wechsler Intelligence Scales for Children, 4th edition - Boston Naming Test - Verbal Fluency Test	Prenatal PCB-153 was not associated with IQ	X
Boucher et al. [66]	Canada, Quebec, Nunavik	8-13 years	248	- cord blood - 14 PCBs - PCB-153	Mean PCB-153: 124.3 μg/kg fat (range: 9.7−653.6)	- Stanford-Binet Copying Subtest - Santa Ana Form Board - Finger Tapping Test	Cord PCB-153 was non-significantly negatively associated with performance on the Finger Tapping Test after controlling for covariates ($P<.10$)	X (↓)
Lyall et al. [67]	USA, California	Not reported	1144 (545 with autism spectrum disorder; 181 with intellectual disability; 418 controls general population)	- maternal serum during pregnancy - 11 PCBs	Median Σ11 PCBs: 57.9 ng/g lipid weight (IQR: 34.9-94.7) Median PCB-153: 7.7 ng/g lipid weight (IQR: 4.5-13.3)	- risk of autism spectrum disorder (ASD) and intellectual disability without autism (ID)	Higher levels of a number of PCBs, particularly PCBs 138/158 and 153 (highest vs lowest quartile) were associated with increased risk of ASD Higher PCB138/158 (2nd and 4th quartiles of exposure) were associated with increased ID risk	↓
Berghuis et al. [54]	The Netherlands	13-15 years	101	- maternal serum during pregnancy - PCB-153 and 3 OH-PCBs in all samples - 9 other PCBs and 3 other OH-PCBs in part of samples	Median Σ10PCBs: 319 ng/g lw (IQR:244.2, 401.1) Median PCB-153: 76.7 ng/g lw (IQR:52.0, 104.6) Median Σ6OH-PCBs: 377.5 pg/g fresh weight (IQR: 276.5, 540.5)	Wechsler Intelligence Scale for Children, third edition, Dutch version (WISC-III-NL) Dutch version of the Rey's Auditory Verbal Learning Test (AVLT) Subtests of Test of Everyday Attention for Children (TEA-Ch-NL) Movement-ABC	PCB-183 levels were near-significantly associated with lower intelligence levels Higher exposure to several PCBs and OH-PCBs was associated with less optimal verbal memory Several OH-PCBs were associated with more optimal sustained auditory attention and more optimal motor balance (more details in Table 2)	↓ & ↑

[a]Negative effects on child outcome indicates poorer outcome, whereas positive effects indicates better outcome.

reported in the Japanese study. In girls, higher prenatal PCB exposure was associated with higher achievement scores on a cognitive test, whereas in boys higher prenatal PCB exposure was associated with less optimal scores on the mental processing scale of the test (this scale intends to measure total intelligence).[52] The negative effects of prenatal PCB exposure on cognitive development found in the Japanese cohort at the age of 6 months, as described in the beginning of this paragraph,[51] were not observed at the age of 42 months. In 4-year-old children in Greece, higher prenatal PCB exposure was found to be associated with less optimal working memory.[58] No associations were found between cord levels of PCB-153 and inattention or activity during testing of fine motor skills in 4-6-year-old children in Canada.[59]

With regard to outcomes in children at school age and early adolescence, five out of the ten studies did not find associations between prenatal PCB exposure and neurodevelopmental outcomes (Table 1). Higher prenatal exposure to PCB-153 was also not found to be associated with parentally assessed motor development in 5-9-years old children in Ukraine, Poland and Greenland, but medium (not high) tertile PCB-153 exposure was found to be positively associated with retrospective parental reports of age at standing-up and walking compared with children with lowest exposure tertile.[60] In the same cohort, higher prenatal PCB-153 exposure was non-significantly associated with a higher prevalence of abnormal scores for conduct at the age of 5-9 years.[61] In a study in the USA, no significant associations were found between prenatal PCB exposure and reading skills at 5 and 8 years of age, and also not with externalizing behavior or intelligence at 8 years of age.[62] Another study performed in the USA, did not find significant associations between prenatal PCB exposure and memory and learning in children aged between 7-11 years,[63] but in the same cohort higher prenatal exposure to PCB-153 was found to be associated with more teacher-reported ADHD-related behavior at the age of 7-11 years.[64] In contrast, higher prenatal exposure to PCBs was found to be negatively associated with ADHD-related behavior in 8- to 10-years-old children living in Germany.[53] In the latter study, higher prenatal PCB exposure was associated with better scores on a parent reported questionnaire on ADHD-related behavior, but conversely with less optimal performance of the children on a subtest on attention.[53] In line with the previous mentioned finding of absent significant associations between prenatal PCB exposure and intelligence in US children at the age of 5−8 years,[62] cord serum levels of PCB-153 were found not to be associated with intelligence in 8- to 14-year-old Canadian children.[65] In the latter mentioned study group, cord PCB-153 levels were non-significantly negatively associated with performances on a fine motor task.[66] A population-based case-control study in the USA including 1144 children studied whether higher prenatal exposure to PCBs was associated with an increased risk for autism spectrum disorder (ASD) or intellectual disability.[67] They found that higher maternal serum levels of PCBs, particularly PCBs 138/158 and PCB-153 were found to be associated with an increased risk of autism spectrum disorder, and that higher PCB 138/158 was also found to be associated with an increased risk for intellectual disability.[67] In the latter mentioned US cohort, the median levels of PCB-153 in maternal pregnancy serum (7.7 ng/g lipid weight; 2000−2003) were lower compared with levels measured in the Dutch cohort (76.7 ng/g lipid weight; 1998−2002),[54] and with levels measured in another European cohort (107, 27 and 11 ng/g lipid respectively in Greenland, Ukraine and Poland; 2002-2004) (Table 1).[60] Comparison of PCBs levels across the different cohorts is difficult because the quantification of exposure levels differs between studies.

Taken together, recent literature suggests that prenatal exposure to PCBs can interfere with neurodevelopmental outcomes in children up to adolescence. At preschool age, higher prenatal PCB exposure has been linked to less optimal performance on cognitive tasks (including psychomotor development, learning and working memory),[51,52,56−58,60] to later reaching of motor developmental milestones,[60] and to more behavioral problems.[55] In contrast, more optimal performance on cognitive tasks was found after higher prenatal PCB exposure in 1.5- and 3.5-year-old girls (not in boys) in two studies in a Japanese cohort.[51,52] At school age, higher prenatal PCB exposure has not been linked to less optimal performance on cognitive tasks in all four recent published cohort studies assessing cognitive tasks,[54,62,63,65] but a case-control study in the USA found that higher prenatal exposure to PCB-138/158 was associated with an increased risk for intellectual disability.[67] Regarding the effects of prenatal PCB exposure on attention at school age, both positive and negative associations were found with ADHD-related behavior.[53,64] The motor development of children at school age and adolescence was not found to be negatively associated with prenatal PCB exposure in all three recent published studies investigating motor

development.[54,60,66] Regarding behavioral problems at school age, both recent published cohort studies reporting on behavioral problems did not find significant associations with prenatal PCB exposure,[61,62] but a case-control study in the USA found that higher prenatal PCB exposure was associated with an increased risk for autism spectrum disorder.[67]

Main findings Dutch cohort- Prenatal exposure to (OH-)PCBs and neurodevelopment

We studied the effects of prenatal exposure to environmental chemicals on neurodevelopmental outcomes in two Dutch birth cohorts. These cohorts were initiated to investigate the effects of exposure to environmental chemicals on child development.[13,50] An overview of the effects of prenatal exposure to PCBs and OH-PCBs on neurodevelopmental outcomes is shown in Table 1.

At follow-up at three months, we found that prenatal exposure to PCBs and OH-PCBs is associated with the quality of the spontaneous motor repertoire in three-month-old children.[68] The first and most important finding is that exposure to high levels of 4-OH-PCB-107 is associated with less than optimal motor development. This suggests that 4-OH-PCB-107 might be more toxic than other OH-PCB compounds, is consistent with the findings in human and animal studies reported by other researchers. A second finding is that higher exposure to some PCBs is associated with reduced age-adequate movements in infants, such as fewer midline movements, less manipulations with their hands and/or feet, and fewer antigravity movements. An exception is 4′-OH-PCB-172, which we found to be associated with more age-adequate movements. A third finding is that higher exposure to PCB-118 is associated more frequently with a cramped movement character. A cramped movement character might be predictive of outcomes later in life - in children with cerebral palsy a cramped movement character at three months was found to be associated with lower levels of self-mobility at school-age.[69]

At the age of three months, we also assessed these infants with an age-adequate neurological examination based on Touwen's method of neurological examination.[70,71] The first and most important finding presented in this study is that higher prenatal exposure to several PCBs is positively associated with neurological functioning. This seems to contradict our previously mentioned findings on motor development, and with the findings in other studies on early neurological development that reported negative associations with neurological functioning.[72] This difference in the direction of associations may be explained by differences in testing measures and/or that other areas and functions of the brain were tested. The assessment of neurological development in the first mentioned study included the observation of the spontaneous motor repertoire, whereas the assessment in the second study included the observation of posture and motility, muscle tone regulation, reflexes and assessment of function of cranial nerves.[70] Another explanation for the differences in the direction of associations may be differences in the levels of exposure. In the Netherlands the exposure levels to PCBs are lower than in populations with a tradition of eating pilot whale blubber as, for instance, the people of the Faroe Islands.[17] We speculated that higher exposure levels might have negative effects, whereas lower levels might possibly have positive effects by stimulating neuronal and/or hormonal processes. A more rapid development might possibly occur at the expense of the formation of stable neural networks. Whether a rapid development at a young age has implications for developmental outcomes later in life is not clear.

A second finding is that 4-OH-PCB-107 is associated with less than optimal neurological functioning in boys.[71] These findings are in line with our findings on spontaneous motor repertoire that also show less optimal outcomes after higher exposures to this compound. In another study, this specific metabolite is also associated with a less optimal mental development in 16-month-old infants.[73]

A third finding is that higher exposure to several PCBs is associated with more optimal visuomotor and sensorimotor functioning in three-month-old children.[71] This suggests that exposure to PCBs possibly has an impact on specific functions of the brain. Studies by other researchers also found relations between prenatal exposure to PCBs and visual functions in children. For example, differences in brain activation were observed on tasks requiring visual processing and manual motor movement in 15-year-old children after prenatal exposure to PCB and methylmercury.[74] Functional magnetic resonance imaging (fMRI) techniques revealed greater and more widespread brain activation in the highly exposed group. This suggests that adolescents with high prenatal exposure require more brain resources to complete tasks and that differential specialization of brain areas may have occurred after prenatal exposure to neurotoxicants.

A final important finding regarding the neurological functioning at three months is that there are sex-specific differences regarding the effects of prenatal exposure to PCBs and OH-PCBs, which suggests that boys are more susceptible than girls.[71] This finding is in line with other studies in animals and humans that also reported that male animals/boys are more vulnerable to the effects of exposure to environmental chemical than female animals/girls.[75,76]

At follow-up at the age of 18 and/or 30 months, we found that prenatal exposure to several organohalogen compounds (OHCs) was associated with mental and motor development.[35] Our most important finding was that OH-PCBs seem to have more effects on neurological development compared with PCBs. Higher exposure to 4-OH-PCB-187 was associated with delayed mental development at 18 months and four OH-PCB congeners and the sum of the measured OH-PCBs correlated positively with mental development at 30 months. A possible explanation for the fact that we did not observe effects of exposure to these OH-PCB congeners at 18 months could be that the effects might be more subtle at younger ages and that their presence becomes more obvious at later ages. The compound 4′-OH-PCB-172 was positively associated with motor development at 30 months, a finding that was consistent with the finding that this compound was positively associated with motor development at the age of three months. Regarding the compound 4-OH-PCB-107, which was found to be negatively associated with neurodevelopmental outcomes at three months, we did not find negative effects on neurological development at 18 months or 30 months. This implies that the negative effects of 4-OH-PCB-107 possibly did not persist into later life, or at least, the effects were not observed with the BSID-II at 18 months or 30 months.

In this study we also found that higher exposure to PCB-153 was, marginally significant, negatively associated with mental development at 18 months.[35] This is in line with other studies that also showed that PCB-153 was more often associated with developmental outcomes in children.[77,78] A possible explanation for the fact that PCB-153 in particular was found to be associated with neurological development is that it is the most abundant PCB-congener. Another explanation could be that PCB-153 can alter neurotransmitter functions that are essential for proper development of the brain, as shown by a decrease in brain serotonin and dopamine in rats.[79]

At follow-up at school age, we found that PCB-153 was associated with less choreiform dyskinesia, and trends towards significance were found with better coordination, but also with more total and more externalizing behavioral problems (Table 2).[36] One of the hydroxylated metabolites of PCB-153, the compound OH-PCB-146, was also found to be associated with more total and externalizing behavioral problems. This might suggest that the hydroxylated metabolite might exert similar action compared with the parent compound. Another explanation can be that the levels of the metabolite are higher in women with higher levels of the parent compound, and that the effects found for the parent compound might be caused by actions of the metabolite. In addition, higher prenatal exposure to OH-PCB-146 was also found to be marginally significantly associated with internalizing behavioral problems and with poorer inhibition, but on the other hand with less choreiform dyskinesia. 4-OH-PCB-107 was found to be associated with poorer fine manipulative abilities at 5 to 6 years of age, this compound was also found to be associated with less optimal motor development in the other Dutch cohort at the age of 3 months.

Because we did find negative effects on neurodevelopment during childhood, we aimed to assess whether these effects persist during later life. We therefore decided to invite the children of both birth cohorts to participate in a follow up study at adolescence, the Development at Adolescence and Chemical Exposure study (DACE-study), and assessed the cognitive and motor outcome in 13 to 15-year-old adolescents.[54] Our first and most important finding was that regarding OH-PCBs, higher prenatal exposure to OH-PCB was associated with more optimal sustained attention and more optimal balance, and that higher exposure to 4-OH-PCB-107 was not associated with motor outcome at adolescence. Previously, in our cohort, the latter compound was found to be associated with less optimal motor development and poorer visuomotor function at three months,[68,71] and poorer fine manipulative abilities at the age of 5−6 years.[36] This suggests that the negative effects of 4-OH-PCB-107 on motor outcomes observed at preschool and school age did not have clinically relevant consequences at adolescence.

Regarding PCB-exposure, our second finding was that only a trend is seen for higher exposure to PCB-183 with lower total intelligence, and that none of the other PCB compounds were associated with borderline/abnormal outcomes on cognitive or motor tasks.[54] Although memory scores were within the range for normal development, higher exposure to PCBs was associated with less optimal verbal memory. This

TABLE 2. Prenatal exposure to (hydroxylated) polychlorinated biphenyls and neurodevelopmental outcomes in a Dutch birth cohort.

Compound	3 months		18 months	30 months	5–6 years	13–15 years
	Motor development (Berghuis et al.)[68]	Neurological functioning (Berghuis et al.)[71]	Mental and motor development (Ruel et al.)[35]	Mental and motor development (Ruel et al.)[35]	Motor, cognitive and behavioral development (Roze et al.)[36]	Motor and cognitive development (Berghuis et al.)[54]
PCB-105	X	↑ (better visuomotor function)	X	X	n.a.	X
PCB-118	↓ (less antigravity movements; cramped movement character)	↑ (better visuomotor function)	X	X	n.a.	X
PCB-138	↓[t] (cramped movement character)	↑ (better visuomotor and sensorimotor functions)	X	X	n.a.	X
PCB-146	X	↑ (higher optimality score; better visuomotor and sensorimotor functions)	X	X	n.a.	X
PCB-153	n.a.	n.a.	X	n.a.	n.a.	X
- RENCO	X	↑ (better visuomotor and sensorimotor functions)	X	X	n.a.	X
- GIC	n.a.	n.a.	↓[t](delayed mental development)	n.a.	↑ and ↓ (less choreiform dyskinesia; better coordination[t]; more total behavioral problems[t]; more externalizing behavioral problems[t])	X
PCB-156	X	↑ (better visuomotor function)	X	X	n.a.	X
PCB-170	X	↑ (better sensorimotor function)	X	X	n.a.	X
PCB-180	X	↑ (better sensorimotor function)	X	X	n.a.	X
PCB-183	X	X	X	X	n.a.	↓[t] (lower total intelligence)
PCB-187	↓[t] (fewer midline leg movements)	↑ (better visuomotor and sensorimotor functions)	X Eerst: ↓ (delayed mental development)	X	n.a.	X
Σ10PCBs	↓[t] (cramped movement character)	↑ (better visuomotor and sensorimotor functions)	X	X	n.a.	X
4-OH-PCB-107	n.a.	n.a.	X	n.a.	n.a.	↑[t] (better sustained auditory attention and better fine motor skills)
- RENCO	↓[t] (lower motor optimality score; reduced repertoire of coexistent movements)	↓ in boys (lower optimality score; worse visuomotor function)	X	↑ (more optimal mental development)	n.a.	♂: ↑[t] (better fine motor skills)

(*continued on next page*)

TABLE 2. (*Continued*)

Compound	3 months		18 months	30 months	5–6 years	13–15 years
	Motor development (Berghuis et al.)[68]	Neurological functioning (Berghuis et al.)[71]	Mental and motor development (Ruel et al.)[35]	Mental and motor development (Ruel et al.)[35]	Motor, cognitive and behavioral development (Roze et al.)[36]	Motor and cognitive development (Berghuis et al.)[54]
- GIC	n.a.	n.a.	X	n.a.	↓ (worse fine manipulative abilities; worse inhibition[t])	X
3'-OH-PCB-138	X	X	X	↑ [t] (more optimal mental development)	n.a.	↑[t] (better static and dynamic balance) ♀: ↑ [t] (higher verbal intelligence)
4-OH-PCB-146	n.a.	n.a.	X	n.a.	n.a.	X
- RENCO	X	X	X	X	n.a.	X
- GIC	n.a.	n.a.	X	n.a.	↑ and ↓ (less choreiform dyskinesia[t]; worse inhibition; more total behavioral problems; more externalizing and internalizing[t] behavioral problems)	X
3'-OH-PCB-153	X	X	X	↑ (more optimal mental development)	n.a.	↑ (better static and dynamic balance) ♀: ↑ [t] (higher verbal intelligence) ♂: ↑[t] (better static and dynamic balance)
4'-OH-PCB-172	↑ (more manipulation)	X	X	↑ (more optimal mental and motor[t] development)	n.a.	♀: ↑ [t] (better static and dynamic balance)
4-OH-PCB-187	n.a.	n.a.	X	n.a.	n.a.	↑ (better sustained auditory attention)
- RENCO	X	X	X	X	n.a.	X
- GIC	n.a.	n.a.	X	n.a.	↓ (worse inhibition)	X
Σ 6 OH-PCBs	X	X	X	↑ (more optimal mental development)	n.a.	X

[t]Trend to significance: $P < .10$; 'n.a.'= not assessed; 'X'= no significant associations; '↓' indicates poorer outcomes and '↑' indicates better outcomes after higher exposure to POPs.

finding was in line with a study on 271 adolescents, aged 11 years to 16 years, that reported that higher prenatal exposure to PCBs was associated with less optimal long-term memory.[80] Our non-significant associations between prenatal exposure to PCBs and attention is in line with most other studies that reported on prenatal exposure to PCBs and attention problems in adolescents.[81–83] In addition, several marginally significant sex-specific associations were found between higher prenatal OH-PCB exposure and more optimal development at adolescence. Higher prenatal exposure to some OH-PCB compounds was associated with more optimal motor development in boys and girls, or with higher verbal intelligence in girls (Table 2). Overall, we concluded that the negative effects of prenatal exposure to PCBs on cognitive and motor outcomes observed at preschool and early school age in our studies (Table 2) did not persist up to and including adolescence, and that prenatal Dutch background levels of PCBs, measured between 1998 and 2002, did not have clinically relevant consequences for cognitive and motor outcomes at adolescence.

Effects of prenatal exposure to (OH-)PCBs on sexual development until toddler age

In Table 3 we provide an overview of the studies on the effects of prenatal (OH-)PCB exposure on reproductive hormone levels in cord or child's serum and sexual development in toddlers (Table 3). All three studies published on the association between prenatal PCB exposure and reproductive hormone levels in cord blood found that higher prenatal PCB levels were associated with lower testosterone levels in cord blood.[84–86]

In a German study, higher levels of cord PCB was found to be associated with lower cord testosterone levels in girls, and to lower cord estradiol levels in boys.[86] Another study on the link between PCB and reproductive hormone levels in cord blood was performed in France. The study found that higher prenatal PCB exposure was associated with lower free testosterone levels (fT), and higher sex hormone-binding globulin (SHBG) in cord serum of male infants, but did not find significant associations with estradiol (E2).[85] Associations between higher prenatal PCB exposure and lower testosterone levels in cord blood were also found in a Chinese study.[84] The authors found that higher prenatal exposure to PCB-28 and PCB-118 was related to lower testosterone levels in cord serum of male infants.[84] In addition, a trend towards significance was found between higher exposure to several individual PCBs (118, 153, 180) and the sum of all 7 measured PCBs and lower cord serum levels of testosterone in the total group. Regarding the effects of prenatal PCB exposure on estradiol levels in the Chinese study, only higher prenatal exposure to PCB-180 was marginally significantly associated with lower estradiol levels in cord blood. Tang et al. was the only study reporting on the associations between prenatal PCB exposure and follicle stimulating hormone (FSH) and luteinizing hormone (LH) in cord blood. They found that higher exposure to one congener (PCB-101) was significantly associated with lower FSH levels in cord serum, and for two other PCBs (28 and 153) and the sum of the seven measured PCBs a similar trend was found.[84] Higher prenatal exposure to PCB-52 was found to be associated with lower LH levels in cord blood in the total group. In cord serum of male infants, the compound found to be associated with lower testosterone levels (PCB-28) was also found to be associated with lower LH levels.

Regarding sexual development in toddlers, three studies have been published on reproductive hormone levels and/or testicular volume (Table 3). The first study was performed in Finland and Denmark, the other two were performed in the two Dutch cohorts described in this review. [87–89] The study by Virtanen and colleagues showed that higher placental levels of PCB WHO-TEQ was associated with higher levels of LH in Finnish 3-month-old boys, whereas no significant associations were found with testosterone, FSH, SHBG or Inhibin B.[87] In contrast, no significant associations were found between prenatal PCB exposure and LH levels in 3-month-old boys in the Netherlands.[88] Higher prenatal exposure to OH-PCB-107 was significantly associated with testosterone levels, and higher prenatal levels of OH-PCB-187 showed a marginally significant association with higher levels of FSH.[88] In the other Dutch cohort, no reproductive hormone levels were measured, but a significant association was found between higher prenatal levels of OH-PCB-153, and a larger testicular volume at the age of three months.[89] Higher exposure to this compound was not found to be associated with testicular volume at the age of 18 months, and none of the other 5 measured OH-PCBs or 10 measured PCB congeners were found to be associated with testicular volume at the age of three or 18 months.[89]

Taken together, higher prenatal PCB exposure has been linked to lower testosterone and estradiol levels

TABLE 3. Overview of studies on the effects of prenatal (OH-)PCB exposure on reproductive hormone levels in cord or child's serum and sexual development in toddlers.

Reference	Location	Sample age at evaluation	n with prenatal PCB data	Prenatal sample	PCB levels	Reproductive hormone levels							Sexual development
						T	fT (T/SHBG)	E2	FSH	LH	SHBG	InhB	Testicular volume
Cao et al. [86]	Germany, Duisburg	Maternal serum and cord blood	60 girls; 45 boys	* maternal blood during pregnancy and milk *Σ 6 PCBs (28, 52, 101, 138, 153, 180); 4 non-o-PCBs; 8 mono-o-PCBs	GM 10^{-3} * Σ 6 PCBs blood: 140 pg/g fat (range: 8-512)	↓ (specific ♀)	n.r.	↓ (specific ♂)	n.r.	n.r.	n.r.	n.r.	n.r.
Warembourg et al. [85]	France, Brittany	Cord blood	282	* cord blood * PCB-153, 187 and Σ3 PCBs (118, 138 and 170)	Median PCB-153: 0.110 μg/L Median Σ 3 PCBs: 0.115 μg/L	X aromatase index =T/E2: ↓	↓ (specific ♂)	X	n.r.	n.r.	↑ (specific ♂)	n.r.	n.r.
Tang et al. [84]	China	Cord serum	76	* cord serum * 7 PCBs (28, 52, 101, 118, 138, 153, 180)	Median Σ PCBs: 2.02 μg L-1 (IQR: 1.13-4.64)	↓ in ♂ for PCB-28 and PCB-118 (↓) for PCB-118, 153, 180 and Σ PCBs	n.r.	(↓) for PCB-180	↓ for PCB-101 (↓) for PCB-28, 153 and Σ PCBs	↓ For PCB-52 and in ♂ for PCB-28	n.r.	n.r.	n.r.
Virtanen et al. [87]	Finland and Denmark	3 months	79 Finnish; 113 Danish boys	* placenta * 37 PCBs	Median PCB-WH-Teq: Finland: 2.15 and 2.12 pg/g fat Denmark: 2.10 and 2.34	X	X	n.r.	X	↑ For PCB WHO-TEq in Finland	X	X	n.r.
Meijer et al. [88]	The Netherlands	3 months	55 boys	* maternal serum during pregnancy * PCB-153, 3 OH-PCBs (107, 146 and 187)	Median PCB-153: 64 ng/g lipid Median OH-PCB-107: 25 pg/g serum	↑ for OH-PCB-107	(↑) for OH-PCB-107	X	(↑) for OH-PCB-187	X	X	X	X not with testicular volume
Soechitram et al. [89]	The Netherlands	3 and 18 months	49 boys	*maternal serum during pregnancy * 10 PCBs (105, 118, 138, 146, 153, 156, 170, 180, 183, 187) and 6 OH-PCBs (107, 138, 146, 153, 172, 187)	Mean Σ 10 PCBs: 308.9 ng/g lipid Mean Σ 6 OH-PCBs: 0.42 ng/g serum	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	↑ testicular volume at 3 months for OH-PCB-153

'↑' and '↓': indicates that higher prenatal PCB exposure is associated with respectively higher and lower hormone levels with $P<.05$; arrows between brackets means $P<.10$; '-' means no associations found; 'n.r.'means not reported.

in cord blood. One Chinese study also showed that higher prenatal exposure to some PCB congeners was associated with lower FSH and LH levels in cord blood. In toddlers, higher prenatal exposure to PCBs was found to be associated with higher LH levels, but not with testosterone or estradiol levels. Higher prenatal exposure to some OH-PCB congeners was found to be associated with higher testosterone and FSH levels and with larger testicular volume in Dutch toddlers.

Effects of prenatal exposure to (OH-) PCBs on pubertal development

In total, we found nine studies reporting on the effects of prenatal PCB exposure on reproductive hormone levels, pubertal stages and/or testicular volume in children at (peri-)pubertal age (Table 4). None of the studies reported significant associations between higher prenatal PCB levels and testosterone levels or testicular volume. Regarding pubertal stage, two studies suggested earlier onset after higher prenatal PCB exposure,[90,91] whereas two other studies found negative associations between prenatal PCB levels and pubertal stage.[92,93]

In the first mentioned study in Table 4, Rennert and colleagues assessed both prenatal PCB levels and the reproductive hormones testosterone and estradiol in German children aged 6-7 and 8-9 years, but the reproductive hormone levels were under the limit of detection in most of the children.[94] In a Taiwanese study in 8-year-old children, all 19 girls prenatally exposed to higher levels than median of the sum of three indicator PCBs (138, 153 and 180) had the pre-pubertal genital stage 1, whereas 4 out of the 14 girls with levels below the median already had genital stage 2.[92] In the latter mentioned study, the sum of the three PCBs was not found to be associated with testosterone, estradiol, FSH or LH. In a Russian study including 489 mother-son pairs, higher maternal serum PCB levels 8-9 years after pregnancy were associated with an earlier pubertal onset of their sons defined by genital stage 2 or higher.[90] In this study, higher maternal PCB-levels were not found to be associated with pubic hair stage 2 or higher, or with a testicular volume larger than 3 mL. In a study performed in California, USA, higher maternal pregnancy serum PCB levels were found to be associated with higher FSH levels in 12-year-old boys, whereas no associations were found with testosterone or estradiol.[95] In another study performed in the USA, including 10- to 15-year-old children from North Carolina, no significant associations were found between prenatal PCB exposure and stage of pubertal development, as assessed through annual mail questionnaires.[91] In a Taiwanese cohort, the pubertal development of children born to mothers with signs and symptoms of 'Yucheng' oil disease or a history of consumption of the contaminated oil, was compared with the pubertal development of unexposed controls.[96,97] In boys, the serum estradiol levels were marginally significantly higher in Yucheng boys at the age of puberty (≥ 13 years) compared with unexposed controls.[96] In girls born to exposed Yucheng mothers, the serum estradiol levels also were significantly higher compared with 13- to 19-year-old girls born to unexposed mothers.[97] Serum levels of FSH were marginally significant higher in exposed girls compared with unexposed controls. Serum levels of testosterone and LH were not significantly different for children born to exposed Yucheng mothers compared with unexposed controls. Finally, in a Faroese birth cohort, higher levels of PCBs in cord *tissue* were not associated with reproductive hormone levels and pubertal development in 156 14-year-old boys,[98] but higher levels in cord *blood* were found to be related to a lower stage of pubic hair in 433 14-year-old boys.[93] In addition, higher levels of PCBs in cord blood were found to be marginally significantly associated with lower testosterone and LH levels and with higher SHBG levels in the 14-year-old boys.[93]

Taken together, no significant associations were found between higher prenatal PCB exposure and testosterone levels at (peri-)pubertal age in the studies included in Table 4. Some studies suggest an association between higher prenatal exposure to PCBs and higher estradiol or higher FSH levels in boys and girls at pubertal age. Regarding development of pubertal characteristics, some studies found that higher prenatal PCB exposure was associated with lower pubertal stages, whereas another study found an association with earlier pubertal onset.

Main findings Dutch cohort- Prenatal exposure to (OH-) PCBs and sexual/pubertal development

At follow-up at adolescence, we found in our Dutch cohort that prenatal exposure to PCBs can advance pubertal development in both boys and girls, based on both biochemical and clinical findings[99] (unpublished results, manuscript under review). The most important finding of this study was that in boys, higher prenatal exposure to PCBs was associated with higher testosterone levels,

TABLE 4. Overview of studies on the effects of prenatal PCB exposure on reproductive hormone levels and pubertal development in children at (peri-)pubertal age.

Reference	Location	Sample age at evaluation	n with prenatal PCB data	Prenatal sample	PCB levels	Reproductive hormone levels							Pubertal stage	
						T	fT	E2	FSH	LH	SHBG	InhB	Tanner Stage	Testicular volume
Rennert et al. [94]	Germany, Duisburg	6-7 and 8-9 years	49 boys; 48 girls	* maternal blood during pregnancy * WHO2005-TEq PCB	GM PCB WHO2005-TEq: 6.30 pg/g blood (fat basis) (range: 1.43-25.47)	n.r. (samples <LOD)	n.r.	n.r. (samples <LOD)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Su et al. [92]	Taiwan	8 years	23 boys; 33 girls	* placental tissue * Σ PCBs TEQ * Σ indicator PCBs: sum of PCB-138, 153 and 180	Median Σ PCBs TEQ: 2.8 pg WHO98-TEQ/g lipid (range: 0.5-6.3) Median Σ indicator PCBs: 22.6 ng/g lipid (range: 5.9-76)	X	n.r.	X	X	X	n.r.	n.r.	♀: greater proportion in G1	n.r.
Humblet et al. [90]	Russia, Chapaevsk	8-13 years (incl. 4 years of follow-up)	489 boys	* maternal serum 8-9 years after pregnancy * Σ PCBs: sum of 6 M-PCBs and 31 ND-like PCBs	Median Σ PCBs: 260 ng/g lipid (IQR: 196- 362)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	Earlier pubertal onset: ≥G2 (not with ≥P2)	X (not with volume >3 mL)
Eskenazi et al. [95]	USA, California	12 years	86 boys	* maternal serum during pregnancy or at delivery * Σ PCBs: sum of 20 PCBs	Median Σ PCBs: 65.8 ng/g lipid (IQR: 43.3-100.3)	X	n.r.	n.r.	↑	X	n.r.	n.r.	n.r.	n.r.
Gladen et al. [91]	USA, North Carolina	10-15 years (plus 1-5 years of follow-up)	278 boys; 316 girls	* maternal serum and/or milk at birth * transplacental PCB index: estimate of maternal PCB levels, average of levels in available samples	Median transplacental PCB index: 1.7 ppm milk fat (range: 0.5-5.5)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	X (♀: tendency to mature earlier)	X
Hsu et al. [96]	Taiwan	11-14 years	121 boys (60 exposed; 61 unexposed controls)	* No PCB measurement; mothers with signs and symptoms of the 'Yucheng' oil disease, or a history of consumption of the contaminated oil	Prenatal PCBs not measured	X	n.r.	(↑) in boys ≥ 13 yr	X	X	n.r.	n.r.	X	X
Yang et al. [97]	Taiwan	13-19 years	38 girls (20 exposed; 18 unexposed controls)	* No PCB measurement; mothers with signs and symptoms of the 'Yucheng' oil disease, or a history of consumption of the contaminated oil	Prenatal PCBs not measured	X	n.r.	↑	(↑)	X	n.r.	n.r.	n.r.	n.r.
Mol et al. [98]	Faroe Islands	14 years	156 boys	* cord blood * Σ PCBs: twice the sum of PCB-138, 153 and 180	GM Σ PCBs: 1.96 ng/g (IQR: 1.14-3.38) and 1.82 ng/g (IQR: 1.09-3.69)	X (visual inspection ↑)	n.r.	n.r.	X	X	X	X	X	X
Grandjean et al. [93]	Faroe Islands	14 years	433 boys	* cord blood * Σ PCBs: twice the sum of PCB-138, 153 and 180	GM Σ PCBs: 1.93 ng/mL (IQR:1.16−3.16)	(↓)	n.r.	n.r.	X	(↓)	(↑)	X	↓ Pubic hair stage (↓) Genital stage	X

'↑' and '↓': indicates that higher prenatal PCB exposure is associated with respectively higher and lower hormone levels or pubertal stage with $P<.05$; arrows between brackets means $P<.10$; 'X' means no significant associations found; 'n.r.'means not reported.

higher Tanner stages for pubic hair, larger testicular volume and change of voice at a younger age. This is in contrast with findings in the study by Grandjean et al. with even higher exposure levels, reporting weak, non-significant inverse associations between prenatal exposure to PCBs and Tanner stage for testicular volume.[93] Our findings imply that even relatively low prenatal exposure to PCBs might interfere with pubertal development.

In girls, higher prenatal exposure to PCB-153 was associated with a higher Tanner stage for pubic hair.[99] A possible explanation for this finding might be an increase in production of adrenal androgens, because those are mainly responsible for growth of pubic hair in girls. A study in a human in−vitro-model showed that several chemicals disturb adrenal steroid genesis, but the effects of PCBs were not assessed in that study.[100] What needs to be clarified is whether the effects of PCB-153 on the development of pubic hair, as we found in our study, could be explained by disturbances of adrenal androgen levels during puberty.

Another finding presented in this study at adolescence was that OH-PCBs seem to have less effect on pubertal development than PCBs, although associations were found for some OH-PCBs.[99] Regarding OH-PCBs, negative correlations with FSH and Inhibin B were observed in girls, and some associations with pubertal characteristics (unpublished results, manuscript under review). Higher exposure to 4-OH-PCB-107 showed a trend toward a higher Tanner stage for pubic hair in boys, and was associated with first ejaculation at an older age. In boys included in the GIC cohort, this compound was found to be positively associated with testosterone levels at the age of three months (Table 3).[88] This suggests that 4-OH-PCB-107 can interfere with hormonal processes early in life, with possible consequences for later life, for example, earlier onset of puberty or faster development of pubertal characteristics. The compound 4-OH-PCB-187 was associated with smaller testicular volume in 13 to 15-old boys, which might be due to an LH/FSH imbalance, because the latter stimulates the Sertoli cells that are responsible for a large part of the testicular volume. A positive trend was found for this compound with follicle stimulating hormone (FSH) at the age of three months (Table 3).[88] Clarification is needed as to whether the effects of prenatal exposure to OH-PCBs found in our study can be explained by the disturbance of sex hormone levels during puberty. The findings in our follow-up at adolescence[99] underline that exposure to environmental chemicals can play a role in the secular trend towards earlier pubertal timing that has been observed during the last decades.[43]

Comparing studies

Comparing results of different longitudinal birth cohort studies around the world is difficult for several reasons. The studies summarized in Tables 1 and 3 of this review used for example different methods for assessment of prenatal exposure to PCBs. The outcome measures also differed between the studies, including whether the development of the children was assessed by a direct measurement (including testing at the clinic), or by an indirect measurement (including assessment by a parent or teacher). Larger studies and more collaboration between investigators of the longitudinal cohort studies might contribute to better understanding of the impact of prenatal exposure to chemicals on child development around the world.

Measurement of prenatal exposure to POPs

To assess prenatal exposure to POPs we used maternal serum samples taken during the third trimester of pregnancy in our Dutch studies. The levels of PCBs and OH-PCBs measured during pregnancy correlated highly with the levels measured in cord blood samples,[101] which is a reflection of the levels to which the fetus is exposed. Because PCBs accumulate in fatty tissue, PCB-levels in the human body increase over time. Degradation products of PCBs, such as hydroxylated metabolites, are excreted via urine. On account of the fact that PCBs are stable compounds that are not readily excreted, we used serum samples rather than urine samples to assess the levels of PCBs in the mothers during pregnancy. In our studies we also measured the hydroxylated metabolites of PCBs in maternal serum samples. Only recently has a technique become available that measures OH-PCBs in human urine samples.[102] In the occupationally exposed German cohort, the investigators found that mainly metabolites of lower chlorinated PCBs were excreted in urine at the highest concentrations. Based on their findings, they concluded that the determination of urinary OH-PCBs might be a suitable biomarker of exposure to lower chlorinated PCBs.[102] Because we also aimed to determine levels of more stable, higher chlorinated PCBs, we believe that measurement in serum samples was the most suitable available method for our studies.

The strengths and limitations of the Dutch cohort study

A major strength of the studies of our Dutch birth cohort is that we assessed neurological development up to 13 years−15 years after birth, which provided us with the opportunity to properly assess long-term effects of prenatal exposure to environmental chemicals. A second strength of our studies is that the children came to our clinic for assessment of neurological outcomes. We used standardized tests administered by trained examiners, thus providing a more robust insight into the performances of the children than the impression of their performances if assessed by parents or teachers.

The studies had several potential limitations. The first limitation is the possibility of Type 1 errors due the explorative nature of the studies. Nevertheless, we believe that our analyses were justified as part of a careful evaluation of a rich data set in hypothesis-driven research.[103] A second limitation concerns sample sizes. Despite the relatively small sizes of our samples, we are of the opinion that the sizes are appropriate for such complicated studies that involve the assessment of several OHCs. A third limitation is the possibility of bias on account of the way we recruited the pregnant women. Women who were willing to participate in a study on the effects of exposure to chemical substances might be more conscious of their lifestyle and eating habits and might possibly adapt their lifestyle, which might have lowered their exposure to POPs. As a consequence, the true effects on neurological developmental and endocrine development in our study group might have been underestimated in comparison to the general Dutch population that might have had even higher levels of exposure levels. A final limitation is that we cannot exclude the possibility that exposure to other POPs confounded our findings. Nevertheless, it seems implausible that these pollutants were associated with some specific PCB metabolites, for example, 4-OH-PCB-107, but not with other compounds in our study. On account of these limitations our studies should be considered explorative and our results should be interpreted with caution. We call for larger studies to confirm our findings.

Conclusion, implications and future perspectives

Prenatal exposure to PCBs interferes with normal child development, not only during the perinatal period, but up to adolescence.

Although legislation has led to prohibition of PCB use in the industry, PCBs are still found in measurable levels in all environmental media and in the human body.

The effects of PCBs on neurodevelopmental outcomes are, although with different size effects, mostly consistent throughout different studies, suggesting less optimal development after higher prenatal PCB exposure. The effects of prenatal exposure to PCBs on pubertal development has not been studied extensively so far. The scarce number of studies showed inconsistent results: some studies suggest more advanced pubertal development after higher PCB exposure, whereas other studies suggest the opposite.

Although legislation has led to prohibition of PCB use in the industry, PCBs are still found in measurable levels in all environmental media and in the human body.

Neurotoxic effects of environmental chemicals

This review shows that prenatal exposure to (background) levels of PCBs and OH-PCBs can interfere with children's neurological development. Although the observed effects in our Dutch cohort study fall within the range for normal development, the literature shows associations between higher prenatal chemical exposure and less than optimal development at different ages, using different testing methods. It is of note that in the more recent literature, associations between PCB exposure and cognitive function at school age were less frequently found. Perhaps the effects at earlier ages are weakened by other more important determinants such as socioeconomic background and education. Another explanation for the fact that recent studies did not find effects of prenatal PCB exposure might be that the levels of PCBs were lower in more recent studies because of declining levels over the years.

The findings presented in this review imply that even relatively low prenatal exposure to PCBs might interfere with neurological development. This raises grave concern about the effects of man-made compounds on child development and it underlines the importance of exercising extreme caution when it comes to using

existing chemicals and to introducing new ones. Besides the insights our studies provide into the prenatal effects of chemical exposure on neurodevelopmental outcomes, new questions also have arisen. For example, there is a question whether postnatal chemical exposure continues to interfere with development during adolescence. Future studies should therefore also focus on levels of chemical exposure during adolescence and whether such postnatal exposure interferes with neurological development and pubertal development. PCBs are already banned by law, but there is growing evidence that other chemicals, such as bisphenol A, may have endocrine disrupting effects. Future studies should therefore also focus on the effects of these newly produced chemicals.

Mechanisms of PCB toxicity

Previously, we found that PCBs can interfere with thyroid hormone metabolism during fetal life, and we suggest that reduction of D3 activity might play a role in PCB toxicity in humans.[101] Because thyroid hormones are essential for the developing brain, disturbances of thyroid hormone metabolism system might be an underlying mechanism for the neurotoxic effects of PCBs. Besides interference with endocrine mechanisms, there is growing evidence for interference of environmental chemicals with epigenetic mechanisms.[104] Epigenetic changes (changes in gene expression not involving changes in gene sequence or structure, like DNA methylation, histone modifications and microRNAs) could underlie long-lasting adverse effects of endocrine disrupting chemicals (as reviewed by Jacobs and colleagues).[104] Experimental animal studies have shown that these adverse effects can be transmitted to unexposed generations. Jacobs and colleagues conclude from their extensive review that epigenetic changes have great potential to become useful for chemical risk assessment as early markers of adversities later on in life or in subsequent generations.[104] Further research is needed to explain whether the effects of prenatal chemical exposure on developmental outcomes we found in our studies can be explained by underlying changes in epigenetic mechanisms.

Environmental chemicals and advanced pubertal development

This review also demonstrated that prenatal exposure to environmental chemicals can advance pubertal development in both boys and girls. This is an important finding with possible consequences for later life, because relations were found between pubertal development and risk of cancer. In girls, an earlier onset of pubertal development was found to be related to breast cancer.[46,47] In boys, late sexual maturation was found to be related to a reduced risk of prostate cancer in adulthood.[105] Future studies should focus on whether our findings of advanced pubertal development after higher prenatal chemical exposure might have consequences later in life, including the risk of cancer and infertility. Another question raised by the effects of chemical exposure on pubertal outcomes, is whether these effects were caused by disturbances of hormone levels. Addressing this question might be valuable in understanding the underlying mechanisms of the effects of exposure to environmental chemicals on pubertal outcomes.

Implications on legislation

Although the production and use of PCBs were banned by law in 1985, PCBs were detected in every one of the 190 serum samples of the pregnant women included in the two Dutch birth cohorts between 1998 and 2002.

The finding that exposure to man-made compounds can interfere with child development as long as 13 to 15 years after exposure is alarming.

The finding that exposure to man-made compounds can interfere with child development as long as 13 to 15 years after exposure is alarming.

We believe that it is of utmost importance that legislation of PCB use is reinforced and that governments continuously monitor and improve their policies on cleanup and disposal of PCB remediation waste in the environment.

The findings in the studies included in this review, together with the findings in the Dutch cohort, demonstrate that prenatal exposure to PCBs can interfere with normal child development, not only during the perinatal period, but up to and including adolescence. These findings further contribute to the awareness of how environmental chemical compounds can interfere with child development and negatively influence healthy ageing.

Conflict of interest

The authors declare that they have no conflicts of interest.

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